## REMARKS

Reconsideration and allowance are respectfully requested.

Claims 9-11 are pending. In a telephone interview, the Examiner confirmed that all previously submitted amendments were entered.

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing the legal standard provided in *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. A claim directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 9-11 were rejected under Section 103(a) as allegedly unpatentable over Mistrello et al. (Immunopharm. 10:163-169, 1985; hereinafter "Mistrello") in view of Hashimoto et al. (GB 2246350; hereinafter "Hashimoto") or Lenardo (WO 94/28926; hereinafter "Lenardo"). Applicants traverse because the cited documents fail to render obvious the treatment of uveitis with 3-(2-ethylphenyl)-5-(3-methoxyphenyl)-1H-1,2,4-

triazole. If the compounds disclosed in Mistrello are not taught or suggested in Hashimoto or Lenardo, why would it be obvious to use Mistrello's compound to treat uveitis?

Mistrello discloses the claimed compound (ST1959/DL111-IT). It reports results on experimental models that can be predictive for the compound's therapeutic application in treating autoimmune diseases, organ transplantation, and cancer. The compound is administered to mice in the following concentrations: 1 mg/kg, 2 mg/kg, 5 mg/kg, 25 mg/kg and 100 mg/kg (see values in Tables I-VII). Mistrello is silent on uveitis.

The doses administered in Mistrello are higher than the dose (i.e., 0.25 mg/kg) that Applicant teach in the present specification. There is no indication in Mistrello for the appropriate dose to treat uveitis. How would the skilled artisan know to administer an effective amount to treat uveitis from the teachings of the prior art?

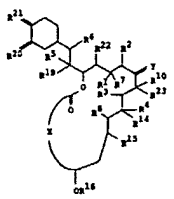
Hashimoto discloses tricyclic compounds of the formula at page 2, lines 20-35, which have immunosuppressive activity (page 8, line 23). Hashimoto discloses that they can be used in the treatment of autoimmune diseases (page 8, line 29) including uveitis (page 8 line 32). But no pharmacologic data are reported and the only working example is a preparation method (from page 10, line 19, to page 12, line 21). Thus, Hashimoto is not enabling for the treatment of autoimmune diseases, more specifically uveitis, since they do not demonstrate pharmacologic effects and, thus, do not indicate that DL111-IT can be used for treating uveitis. Moreover, there is no indication in Hashimoto of what kind of modification to the extremely complex structure of the tricyclic compounds would maintain efficacy in treating uveitis. One of ordinary skill in the art reading Mistrello and Hashimoto would understand that a compound having immunosuppressive activity is not automatically effective in treating both immune and autoimmune diseases. An accurate reading of Mistrello reveals that DL111-IT, alias ST1959, the compound used in the present application is active in experimental models which *might be of predictive value* for its therapeutic application in clinical medicine (see "Discussion" section). One of ordinary skill in the art would weight these words with great care since there is no clear teaching that DL111-IT *has* a clinical value in treating uveitis. The common knowledge in the art of medicine has established that a potential candidate for use in medicine *must* demonstrate its efficacy in clinical study, as also established in USPTO practice.

Laboratory animals are a valid model when tested on the same disease to be treated in humans. The authors of the Mistrello document were very cautious in declaring clinical applications for DL111-IT because of such considerations. In fact, they demonstrated a clinical application only for skin graft rejection. The latter immune reaction, however, is not an autoimmune disease since the experimental model was carried out with an allo-graft. Therefore, Mistrello does not give a clear and unmistakable indication that DL111-IT would be effective in treating autoimmune disease, in particular uveitis.

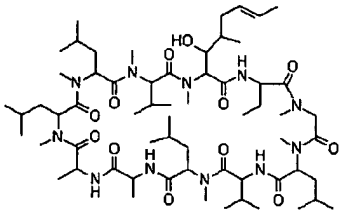
Starting from Mistrello, one of ordinary skill in the art would search for help in the art. Hashimoto disclose tricyclic compounds with a chemical structure that is extremely far from DL111-IT. Hashimoto pronounces effectiveness of the tricyclic compounds as immunosuppressive agents. It discloses they are useful in the treatment of resistance to transplantation of organs or tissues, graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases, such as rheumatoid arthritis, systemic lupus erhytematosus, Hashimoto's diabetes, uveitis, such as Behcet's disease, etc (Hashimoto, page 8, last paragraph). But there is no demonstration, much less animal testing, of any pharmacologic activity. Therefore, one of ordinary skill in the art would bear the burden of undue experimentation to test the compounds provided by Hashimoto with no expectation of success that they would effectively treat uveitis.

For this reason, Hashimoto does not remedy the deficiencies of Mistrello in failing to render obvious Applicants' claimed invention.

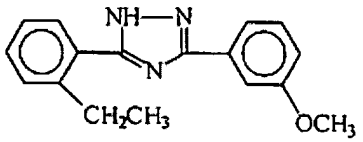
Moreover, the fact that Hashimoto discloses other immunosuppressive agents is irrelevant to constructing a prima facie case of obviousness because Hashimoto's compounds are not structurally related to the compound of the present invention. One of ordinary skill would find no guidance in Hashimoto on modifying the tricyclic compounds disclosed therein to arrive at the claimed DL111-IT compound. Hashimoto's compound is more similar to cyclosporin A than DL111-IT (see below).



Hashimoto



Cyclosporin A



DL111-IT = ST1959

From such a comparison, one of ordinary skill in the art would have been more likely to use a compound like Cyclosporin A than to DL111-IT in treating autoimmune disease. Cyclosporin A is specifically active in suppressing T-cell function (Mistrello et al., page 163, last paragraph of left column to first paragraph of right column). Instead, Applicants teach in the present applications that a a compound is needed with a *specific and selective* activity on T cells, in particular γδ T cells (see "Background" section). Therefore, based on the combination of Mistrello and Hashimoto, one of ordinary skill in the art might have tried to use Hashimoto's compounds or even Cyclosporin A to treat uveitis with no reasonable expectation of success. But the use of DL111-IT to effectively treat an autoimmune disease, specifically uveitis, would not have been obvious.

Lenardo discloses that autoimmune diseases can be treated by administering IL-2 (interleukin) together with the antigen which is specifically involved in the disease (page 1, lines 11-13). This treatment is to be practiced by a precise protocol comprising cyclic administration of the antigen, capable of challenging the T cell, then administering IL-2 when the T cell expresses high level of IL-2 receptors and, finally, re-administering the same antigen so as to cause T-cell apoptosis (programmed death) (see claim 2; page 5, line 31; page 6, line 16). Lenardo reports a working example for experimental allergic uveitis (EAU) (page 39 of Example 3). This example emphasizes that only mice that were repetitively inoculated with IRBP (the protein which causes the onset of EAU) together with IL-2 were protected from the disease. Lenardo refers to the ability of co-administration of IL-2 and IRBP to prevent allergic uveitis. But IL-2 is a cytokine (i.e., a protein), whose structure is far different from the DL111-IT compound of the present invention. For this reason, the findings on IL-2 cannot be applied to DL111-IT. Moreover, IL-2 is effective only when it is co-administered with the antigen. In contrast, DL111-IT can be used alone (i.e., without antigen) to effectively treat uveitis.

Lenardo also teaches, "The key feature [...] is that only the antigen-specific T cells which are a small component of the patient's T cell repertoire would be eliminated. The treatment would leave the patient's immune system largely intact. This is in contrast to the present treatments that rely upon general immunosuppression that seriously incapacitates the host's immune function." Therefore, one of ordinary skill in the art, with the task of finding selective and less toxic immunosuppressants, as correctly said by the Examiner on page 5 of the pending Office Action, would start from Lenardo, which is the most promising piece of art for treating uveitis. Lenardo teaches that general immunosuppression is to be avoided. In the search for an alternative treatment, one of ordinary skill in the art would not use Mistrello's compound because general immunosuppressive agents such as DL111-IT (the abstract teaches its "significant immunosuppressive activity both on humoral and cellular immunity") would not be desirable.

Furthermore, one of ordinary skill in the art starting from Lenardo would never have arrived at the claimed invention, which does not provide a first challenge with the specific antigen, the administration of the drug and the second challenge with the same antigen. The claimed method only provides administration of the DL111-IT compound. Nothing in Lenardo suggests that the treatment could be successful by eliminating the twice antigen administration. To the contrary, antigen administration is strictly necessary according to Lenardo.

Neither Hashimoto nor Lenardo fill in the gaps between Mistrello and the present invention. In view of the foregoing, claims 9-11 are patentable over Mistrello in view of Hashimoto or Lenardo.

Claims 9-11 were rejected under Section 103(a) as allegedly unpatentable over Rossi (WO 98/55463; hereinafter "Rossi") and Hashimoto or Lenardo, in further view of Kawahito et al. (J. Immunol. 161:4411-4419, 1998; hereinafter "Kawahito"). Applicants traverse because this rejection also suffers from the deficiencies noted above. Neither Mistrello nor Rossi teach or suggest the treatment of uveitis.

Rossi discloses that ST1959, alias DL111-IT, has an antigestative effect (page 3). The working examples report termination of pregnancy in rats (pages 20-21), immunosuppressant activity in mice (pages 23-26), and effects on a skin graft (pages

26-27) and choriocarcinoma (pages 27-28). Moreover, ST1959 is used as reference compound, to evaluate the effect of 3-(2-decanoyl-oxymethylphenyl)-5-(3-ethoxy-phenyl)-1H-1, 2, 4-triazole (i.e., compound VI). The compounds of Rossi are more effective in inducing the termination of pregnancy than the reference compounds (page 21) and they are able to reduce auto-antibody production as well as to prolong the skin graft survival (page 23). Therefore, Rossi adds nothing more than Mistrello and the same considerations for why the present invention is patentable apply here although they are not repeated.

As previously discussed, Hashimoto does not enable the treatment of uveitis. It also does not permit one of ordinary skill in the art to arrive at Applicants' claimed invention by starting from Rossi. Hashimoto relates to a different class of compounds (i.e., not ST1959). At best, one of ordinary skill in the art would be led to using a different class of compounds without a reasonable expectation of success.

As previously discussed, Lenardo discloses the prevention of allergic uveitis by administering the combination of IL-2 and IRPB at different times. It also does not permit one of ordinary skill in the art to arrive at Applicants' claimed invention by starting from Rossi. At best, it teaches away from the use of ST1959 in treating uveitis.

Kawahito relates to the genetic factors associated with autoimmune disease. Although it discloses that a region on chromosome 4 is involved in autoimmune uveitis, there is no reason to believe from such data that a compound effective in treating diseases as taught by Rossi would be effective in treating an autoimmune disease, much less uveitis. Kawahito does not remedy the failures of Rossi and Hashimoto OR Rossi and Lenardo to render obvious the claimed invention. In view of the foregoing, claims 9-11 are patentable over Mistrello in view of Hashimoto or Lenardo.

Withdrawal of the Section 103 rejections is requested because the claims would not have been obvious to one of ordinarily skill in the art when this invention was made.

*Conclusion*

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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